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10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024	4092

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EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
01/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,205	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 56-98* is/are pending in the application.

4a) Of the above claim(s) *13-35 and 67-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 56-66, and 82-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 03 Oct 2008, in which claims 1, 2, 11, 13, 14, 23, 25, 26, 56-67 and 82 are amended to change the scope and breadth of the claim.

This application is the national stage entry of PCT/US04/09387, filed 26 Mar 2004; and claims benefit of provisional application 60/458,922, filed 28 Mar 2003; and claims benefit of provisional application 60/484,756, filed 02 July 2003; and claims benefit of provisional application 60/541,247, filed 04 Feb 2004.

The filing date of the instant claims 12, 66, 83, 85 and 89 are deemed to be the filing date of the instant application which is the filing date of PCT/US04/09387, 26 Mar 2004. The filing date of instant claims 1-11, 56-65, 82, 84 and 86-88 are deemed to be the filing date of provisional application 60/541,247, filed 04 Feb 2004.

Claims 1-35 and 56-98 are pending in the current application. Claims 13-35 and 67-81, drawn to non-elected inventions, are withdrawn.

Election/Restrictions

Applicant's remarks regarding the requirement for restriction are moot as the requirement was made FINAL in the Office Action mailed 04 Apr 2008.

As recited in the Office Action mailed 06 Dec 2006, where applicant elects claims directed to the product, and the product claims are subsequently found allowable,

withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

Objections Withdrawn

Applicant's Amendment, filed 03 Oct 2008, with respect to objections to the specification has been fully considered and is persuasive, as the identified informalities are corrected.

This rejection has been **withdrawn**.

Rejections Withdrawn

Applicant's Amendment, filed 03 Oct 2008, with respect to claims 2, 11 and 57 rejected under 35 U.S.C. 112, second paragraph, as being indefinite has been fully considered and is persuasive, as amended claims 2 and 11 recite the complex cladribin-cyclodextrin complex and amended claim 11 recites the definite term of a point on a specifically defined curve on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin and Applicant's remarks regarding the definition of saturated is persusaive.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 03 Oct 2008, with respect to claims 1-5, 11, 56-60, 82-90 and 94-98 rejected under 35 U.S.C. 102(b) as being anticipated by Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) has been fully considered and is persuasive, as Schultz et al. is not seen to disclose the composition comprising no significant amount of free crystalline cladribine therein (amended claim 1) or the complex consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex (amended claim 56) explicitly, implicitly or inherently.

This rejection has been **withdrawn**.

The following are new or modified grounds of rejection necessitated by Applicant's Amendment, filed 03 Oct 2008, in which claims 1, 2, 11, 13, 14, 23, 25, 26, 56-67 and 82 are amended to change the scope and breadth of the claim. Claims 2-12, 57-66 and 82-83 depend from claims 1 and 56 directly or indirectly, and incorporate all limitations therein, including changes to the scope and breadth of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1-12, 56-66 and 82-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, of record).

Schultz et al. discloses a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin (column 2, lines 31-39). The disclosed product is substantially identical to the product-by-process. Schultz et al. discloses the use of β- and γ-cyclodextrins (column 2, lines 56-58) and derivatives wherein one or more cyclodextrin hydroxy groups are replaced with groups such as methyl, hydroxypropyl, carboxymethyl (column 3, lines 26-27) or sulfobutylcyclodextrins (column 4, lines 22-24). The phrase "one or more cyclodextrin hydroxy groups" combined with the absence of specific structural details of which hydroxyl group is substituted with a methyl group meets the limitation of "randomly methylated β-cyclodextrins". Schultz et al. discloses the solid oral dosage form in the form of a tablet (column 5, lines 37-38) including the

excipients sorbitol and magnesium stearate (column 6, lines 2-7), disclosing a product that is substantially identical to a product-by-process meeting the limitations of the instant claims invention. Schultz et al. discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, which would lead one of skill in the art to instantly envision a cladribine to cyclodextrin ratio ranging from 15 mg:100 mg to 15mg:500 mg, or 1:6.67 to 1:33.3 by weight (column 6, lines 23-31). The instant specification suggests that maximum amount of cladribine which can be complexed gives a weight ratio of 1:10 for the cladribine:cyclodextrin complex. Therefore a composition comprising the cladribine:cyclodextrin complex that contains a cladribine to cyclodextrin ratio of 1:6.67 describes a composition that comprises a "saturated" complex and meets the limitations of instant claims 2 and 57. Schultz et al. incorporates-by-reference the method of making said solid oral dosage form (Schultz et al.column 5, lines 50-52) disclosed in WIPO Publication WO97/18839, Baert et al., which provides evidence in the embodiment wherein the melt-extruded forms consist essentially of amorphous material (Baert et al. page 8, lines 14-15). Therefore Baert et al. provides evidence that it was recognized in the prior art that the product disclosed by Schultz et al. inherently includes amorphous cladribine-cyclodextrin complex in a solid oral dosage form. Schultz et al. implicitly discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, or a cladribine to cyclodextrin ratio ranging from 1:6.67 to 1:33.3 by weight (column 6, lines 23-31).

To address the scientific issue regarding the equilibrium presence of both the inclusion and non-inclusion complex, while the equation for the equilibrium of the

cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex would be different for cladribine and cyclodextrin in a solvent versus cladribine and cyclodextrin in a molten state due to the lack of a solvent, the equilibrium and thus equilibrium products, the cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex, would still be inherent in the product disclosed by Schultz et al.

Schultz et al. does not specifically disclose the composition comprising no significant amount of free crystalline cladribine therein (instant claims 1). Schultz et al. does not specifically disclose the composition corresponding to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin (instant claim 11). Schultz et al. does not specifically disclose the complex consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex (instant claim 56). Schultz et al. does not specifically disclose the composition comprising a cladribine to cyclodextrin ratio from about 1:10 to about 1:16 (instant claims 6, 7, 10, 61, 62 and 65), or a ratio of about 1:14 (instant claims 8 and 63) or about 1:11 (instant claims 9 and 64). Schultz et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b) (instant claims 12 and 66). Schultz et al. does not specifically disclose the product-by-process wherein

12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 91 and 93), to give a cladribine to cyclodextrin ratio of 1:14.38. Schultz et al. does not specifically disclose the product-by-process wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 92), to give a cladribine to cyclodextrin ratio of 1:10.55.

Baert et al. discloses a solid mixture comprising one or more cyclodextrins and an insoluble active ingredient embedded into the cyclodextrin carrier (abstract), and teaches ratios of active ingredient to cyclodextrin of from about 1:100 to 100:1, from about 1:5 and 5:1 and from about 1:3 to 3:1 (page 11, lines 1-5). These ratios are interpreted as mole ratios because Baert et al. teaches the use of different active ingredients with different molecular weights. A mole ratio of active ingredient to cyclodextrin of about 1:3 for cladribine (MW 285.7 g/mol) and β-cyclodextrin (MW 1135 g/mol) gives a ratio by weight of approximately 1:11.9. The ratio of 1:11.9 meets the limitation of both a ratio of about 1:11 and a ratio of about 1:14 according to the non-limiting definition of "about" as a variance of 20% provided in the instant specification page 9, lines 6-11. Such a saturated complex would consist of only (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, and being a saturated complex corresponds to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve

defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin disclosed by Schultz et al. in the ratios of cladribine and cyclodextrin taught by Baert et al. One of ordinary skill in the art would be motivated to combine the Schultz et al. and Baert et al. because Schultz et al. incorporates-by-reference Baert et al. and because Baert et al. suggests that improving a similar product according to the teachings of Baert et al. has beneficial properties such as high bioavailability and dissolution rate (Baert et al. page 7, lines 25-27). One of ordinary skill in the art would have an expectation of success because the ratios taught by Baert et al. fall within the range of ratios that is implicitly disclosed by Schultz et al. Schultz et al. in view of Baert et al. does not teach the specific cladribine to cyclodextrin ratios of 1:14.38 or 1:10.55, however these ratios are encompassed by the prior art and Baert et al. suggests optimization of the ratio (Baert et al. page 11, lines 1-5). See also MPEP 2144.05 II.A, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." One of ordinary skill in the art would be motivated to optimize the cladribine to cyclodextrin ratio to give the composition comprising no significant amount of free crystalline cladribine therein because Schultz et al. teaches undesireable recrystallization of cladribine in tissue may occur and damage the surround tissue and that complexes with cyclodextrin are known

to solubilize the compound (Schultz et al. column 2, lines 1-15). Schultz et al. in view of Baert et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b). However, it is well known in the art that the formation of an inclusion complex from a non-inclusion complex is an equilibrium process, and the position of this equilibrium is dependent on the concentrations of the cladribine and cyclodextrin. This molecular inclusion equilibrium is a process inherent in the formation of the inclusion complex in both aqueous solutions and hot melt liquid mixtures, and Baert et al. teaches variation of the ratio of cladribine to cyclodextrin and hence their relative concentration.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed, namely the position of the equilibrium process governing formation of an inclusion complex and a non-inclusion complex. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claims 82-90 and 94-98 are drawn to a product-by-process. The disclosed product is substantially identical to the instantly claimed product-by-process, an amorphous solid pharmaceutical oral dosage form comprising cladribine and cyclodextrin. "[E]ven though product-by-process claims are limited by and defined by

the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

Response to Applicant's Remarks:

Applicant's Remarks, filed 03 Oct 2008 have been fully considered and not found to be persuasive.

Applicant notes that the method of Baert et al. is drawn to compounds that show no appreciable decomposition at the temperatures needed to melt and extrude the mixture. Applicant provides evidence that cladribine melts with decomposition at 220-235 °C, below the temperatures of the working examples of Baert et al. and below the melting point of HPβCD at 278 °C. This evidence regarding the applicability of the method disclosed by Baert et al. incorporated into Schultz et al. applied to the

disclosure of Schultz et al. has been carefully considered in view of the absence of disclosed working examples within Schultz et al. However it is well known in that art that a mixture of compounds exhibits some magnitude of freezing point depression due to the colligative properties of the mixture (entry for liquid, Britannica Online Encyclopedia, cited in PTO-892), and conversely there is a depression in the melting point. Suzuki et al. 1988 (Chem. Pharm. Bull., 1988, 36(2), p720-725, cited in PTO-892) provides evidence that further freezing point depression is observed for mixtures of butanol and sucrose with cyclodextrins (page 720, abstract and paragraph 2-3) due to the formation of the complex. Suzuki et al. 1993 (Chem. Pharm. Bull., 1993, 41(8), p1444-1447, cited in PTO-892) discloses this freezing point depression is observed in complexes such as barbiturate/CD (page 1444, left column, paragraphs 2-3). Therefore as the evidence provided concerns the melting point of the compounds as pure compounds rather than as the mixture, and in view of the presumption of validity afforded to the issued patent Schultz et al., this remark is not persuasive.

Applicant remarks that Baert et al. teaches the method of Baert et al. gives rise to different products than when said solids are first brought into contact with water or another solvent and then extruded. However, the invention of Baert et al. suggests that the different products given rise to are the solid solutions of the immediately prior statement (page 6, lines 14-15), or a mixture consisting of amorphous material and no crystalline material implied at page 8, lines 10-20.

Applicant's remarks that there is no reason for the interpreting the ratios taught by Baert et al. as mole ratios in view of the teachings of Schultz et al. and the instant

application regarding the disclosure of weight ratios. However, Suzuki et al. 1988 discloses cyclodextrin complexes in terms of the mole ratio (page 722, paragraph 3) and Suzuki et al. 1993 discloses the cyclodextrin complexes in terms of the stoichimetic ratios (page 1444, left column, paragraphs 1-3), or mole ratios. Therefore the prior art teaches both the interpretation as a mole ratio and a weight ratio. Absent a teaching within Baert et al. specifying the type of ratio intended and in view of the use of both mole ratios and a weight ratios in the prior art in the area of cyclodextrin complexes, one of skill in the art would find either interpretation equally reasonable.

Applicant notes that the product made obvious by Schultz et al. in view of Baert et al. is produced by a different process than the instant product-by-process. However, absent factual evidence of how this process necessarily makes a different product, it is found that the amorphous solid pharmaceutical oral dosage form comprising cladribine and cyclodextrin made obvious by Schultz et al. in view of Baert et al. is substantially identical to the same product may be the process of the instant invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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